Alterations of Thyroid Hormone Levels in Cadmium Exposure

Kadmiyum Maruziyetinde Tiroid Hormon Seviyesindeki Değişiklikler

Elevated Thyroid Hormones with Cadmium Toxicity

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Özet

Amaç: Çevresel kimyasallar ve ağır metaller; iyot(I)'un taşınmasının bozulması, tiroid peroksidaz , tiroid hormonu bağlayıcı proteinler, hepatik katabolizma, deiodinaz ve reseptör bağlanmasının bozulması da dahil olmak üzere çeşitli mekanizmalar aracılığıyla tiroid hormon düzeylerini değiştirebilir. Bizim amacımız kadmiyum maruziyetinde tiroid hormon seviyelerindeki değişikliği araştırmaktı. Gereç ve Yöntem: 10 yılı aşkın çalışma süreleri bulunan 18-70 yaş arası çevresel maruziyeti olan boyacılar, kaynakçılar, madenciler ve dökümcüler çalışmaya alındı. Bireyler tam kan kadmiyum düzeylerine göre altı gruba ayrıldı (Grup 1: 0-0.5 µg/L; Grup 2: 0.5-1 µg/L; Grup 3: 1-1.5 µg/L; Grup 4: 1.5-2 µg/L; Grup 5: 2-2.5 µg/L; Grup 6: >2.5 µg/L). Bulgular: Kadmiyum düzeyleri ile serum serbest tiroksin ve triiyodotironin seviyeleri arasında pozitif korelasyon, serum alanine aminotransferaz ve vitamin B12 seviyeleri arasında negatif korelasyon bulundu. Tartışma: Kadmiyum maruziyetinin tiroid hormon düzeylerinde artışa öncülük ettiği saptanmıştır.

Anahtar Kelimeler

Kadmiyum Toksisitesi; Tiroid Fonksiyonları; Tiroksin; İşçi

Abstract

Aim: Environmental chemicals and heavy metals may alter thyroid hormone levels via several mechanisms, including disruption of iodine (I) transport, thyroid peroxi¬dase, thyroid hormone-binding proteins, hepatic catabolism, deiodinases, and receptor binding. Our aim was to investigate the change in thyroid hormone levels in cadmium exposure. Material and Method: Painters, welders, miners, and smelters with an occupational exposure of more than 10 years, aged between 18-70 years, were divided into six groups according to whole blood cadmium levels (Group 1: 0-0.5 µg/L; Group 2: 0.5-1 µg/L; Group 3: 1-1.5 µg/L; Group 4: 1.5-2 µg/L; Group 5: 2-2.5 µg/L; Group 6: >2.5 µg/L). Results: There was a positive correlation between cadmium and serum free thyroxine and triiodothyronine levels. There was a negative correlation between cadmium and serum alanine aminotransferase and vitamin B12 levels. Discussion: Cadmium exposure was found to lead to an increase in thyroid hormone levels.

Keywords

Cadmium Toxicity; Thyroid Functions; Thyroxine; Workers

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Introduction

From the physiological point of view, cadmium does not have a functional role in living organisms. It probably enters the cell via voltage-sensitive Ca+2 and Mg+2 channels of the plasma membrane. Due to its chemical similarity with zinc, it interferes with the physiological functions of zinc [1]. Cadmium (Cd2+) is a heavy metal that is produced due to pollution from several sources. Occupational exposure can result from the amounts released into the environment and from the end-products related to mining, smelting, and electroplating. Also, exposure results from the profound use of consumer products such as nickel/ Cd2+ batteries, pigments, and plastics. Cadmium toxicity is associated with elevated incidences of chronic kidney disease, hypertension, osteoporosis, and leukemia, as well as cancers of the lung, kidney, urinary bladder, pancreas, breast, and prostate [2]. Thyroid hormones (THs) play a critical role in the functions of nervous, reproductive, and cardiovascular systems in both children and adults [3]. Iodothyronine deiodinases constitute a group of selenoproteins which initiate or terminate thyroid hormone action. Three iodotronine deiodinases, D1 and D2, were identified and they are functional in catalyzing the outer and/or the inner ring deiodination in mammals. The Type 1 Deiodinase (D1) is responsible for the removal of iodines from iodothyronines [4]. Although it is highly expressed in various tissues, hepatic D1 activity is generally considered to be the most important source of plasma triiodothyronine (T3) [5].

In recent years, the endocrine-disrupting property of cadmium has been observed many times in animal studies [6,7]. It has been demonstrated that type I 5'-deiodinase (5' DI) levels decrease with exposure to cadmium and other heavy metals [8].

The molecular mechanisms of toxic effects of cadmium have not yet been completely understood [9]. The overall effect is likely to be the synergism of several proposed mechanisms such as oxidative stress [10], apopitosis [11], and interference with cell functions [12].

It has been concluded that cadmium has the affinity to concentrate in the thyroid gland in addition to the liver, kidneys, and pancreas. Whole blood cadmium levels have a positive correlation with thyroid gland accumulation. Cadmium causes oxidative stress and affects the tissue by indirect mechanisms. Mitochondria are considered to be the main intracellular targets for cadmium [13]. Also, the thyroid-disrupting effect of cadmium has been reported as structurally degrading the rough endoplasmic reticulum of this tissue. This process may also lead to inflation in mitochondria [14].

In our study, our aim was to determine the serum thyroid hormone levels and metabolic status of cadmium-exposed workers in several industrial sectors and provide information about cadmium toxicity.

Material And Method

Study Population

The patients who were admitted to Ankara Occupational Diseases Hospital with a suspicion of cadmium exposure ,between January 2011 and December 2013 were included in this study. A total of 1724 participants (517 painters, 344 welders, 431 miners, and 432 smelters) with an occupational exposure more than 10 years and for whom blood cadmium levels for the previous 3-year period were obtained from patient records were included in the study. The subjects with diagnosis of a chronic illness including chronic renal failure, acute or chronic hepatitis, or thyroid disease were excluded. The age range was 18 to 70 years, with a median age of 38 years. The study was approved by the Kecioren Training and Education Hospital Ethics Committee on 22.02.2012 (Approval number: B.10.4.ISM.4.06.68.49).

Sampling and Laboratory Procedures

Fasting whole blood samples were collected from the participants into ethylenediaminetetraacetic acid (EDTA) containing tubes. Whole blood cadmium levels were determined using Inductively Coupled Plasma Mass Spectrometry (ICP-MS) (Agilent 7700 series, Tokyo, Japan). Blood samples were digested by the microwave induced acid digestion method. A standard solution of cadmium was prepared by dilution of certified standard solutions (High-Purity Standards, Charleston, SC, USA). Two levels of quality control materials were used (Seronorm, Billingstad, Norway) [15]. The results were expressed as micrograms per liter. Biochemical parameters (Free T3, T4, TSH, folic acid, vitamin B12, AST, and ALT) were analyzed in Roche Cobas 6000 e601/c501 electrochemiluminescence hybride analyzer (Roche, USA).

All the participants of this study gave informed consent. The participants were classified into six groups according to the whole blood cadmium levels. Group 1: 0-0.5 µg/L; Group 2: 0.5-1 µg/L; Group 3: 1-1.5 µg/L; Group 4: 1.5-2 µg/L; Group 5: 2-2.5 µg/L; Group 6: >2.5 µg/L.

Statistical Analysis

The statistical analysis was performed using SPSS v16 software. The statistical data consists of the median, minimum and maximum blood levels. Kolmogorov-Smirnov test was performed to verify normality and differences between the groups were compared using Kruskal-Wallis and Mann Whitney U tests for non-parametric variables. $p<0.05$ was considered to be significant. Spearman correlation test was performed for whole blood cadmium and serum free T3, thyroxine (T4), Vitamin B12, and ALT.

Results

Biochemical and demographic parameters are presented in Table 1. There was no significant difference for serum thyroid-stimulating hormone (TSH), aspartate aminotransferase (AST), and folic acid levels between the six groups ($p=0.187$, $p=0.193$ and $p=0.467$, respectively). Serum vitamin B12 and serum ALT levels were higher in Group 1 compared to other groups. Serum free T3 and T4 levels were significantly lower in Group 1 compared to other groups ($p<0.001$) (Figure 1).

There was a positive correlation between cadmium and serum free T4 and T3 levels ($r=0.167$, $p<0.001$and $r=0.159$, $p<0.001$, respectively) (Figure 2).

There was no correlation between whole blood cadmium and serum TSH levels (Figure 2) ($r=0.026$, $p=0.826$). There was a negative correlation between cadmium and serum vitamin B12 levels (Figure 2) ($r= -0.112$, $p<0.001$).

Table 1. Biochemical and demographic parameters of all groups.

	Group 1 (n=438)	Group 2 (n=355)	Group 3 (n=372)	Group 4 (n=216)	Group 5 (n=136)	Group 6 (n=207)
Whole Blood Cadmium (µg/L) Median (Min-Max)	0.20 (0.01-0.49)	0.70 (0.50-0.99)	1.20 (1.00-1.48)	1.70 (1.50-1.99)	2.20 (2.00-2.49)	3.30 (2.50-9.80)
Serum TSH (mIU/L) Median (Min-Max)	1.35 (0.33-4.86)	1.42 (0.31-4.98)	1.50 (0.34-4.33)	1.40 (0.31-4.93)	1.39 (0.37-4.49)	1.46 (0.34-4.64)
Serum Free T3 (pg/mL) Median (Min-Max)	3.16 (1.54-4.67)	3.25 (1.20-4.41)	3.34 (1.83-4.89)	3.35 (1.89-4.99)	3.26 (1.36-4.39)	3.37 (1.29-4.73)
Serum Free T4 (ng/dL) Median (Min-Max)	1.16 (0.68-1.71)	1.22 (0.81-1.73)	1.24 (0.82-1.73)	1.23 (0.82-1.71)	1.23 (0.90-1.65)	1.24 (0.85-1.77)
Serum ALT (U/L) Median (Min-Max)	25 (6-163)	22 (7-165)	20 (5-202)	21 (6-152)	22 (6-280)	21 (3-131)
Serum AST (U/L) Median (Min-Max)	21 (5-181)	20 (10-97)	19 (9-190)	19 (10-200)	20 (10-108)	21 (10-68)
Serum Folic Acid (µg/L) Median (Min-Max)	6.30 (1.2-18.3)	6.42 (1.0-15.2)	5.91 (1.5-19.6)	6.14 (2.5-14.7)	6.03 (1.5-20.3)	6.26 (2.4-16.6)
Serum Vitamin B12 (ng/L) Median (Min-Max)	270 (58-1001)	257 (83-1173)	255 (83-1401)	245 (88-1507)	239 (93-837)	234 (93-854)
Age (years) Median (Min-Max)	41 (18-69)	41 (19-72)	39 (18-58)	39 (18-56)	39 (20-54)	39 (20-65)

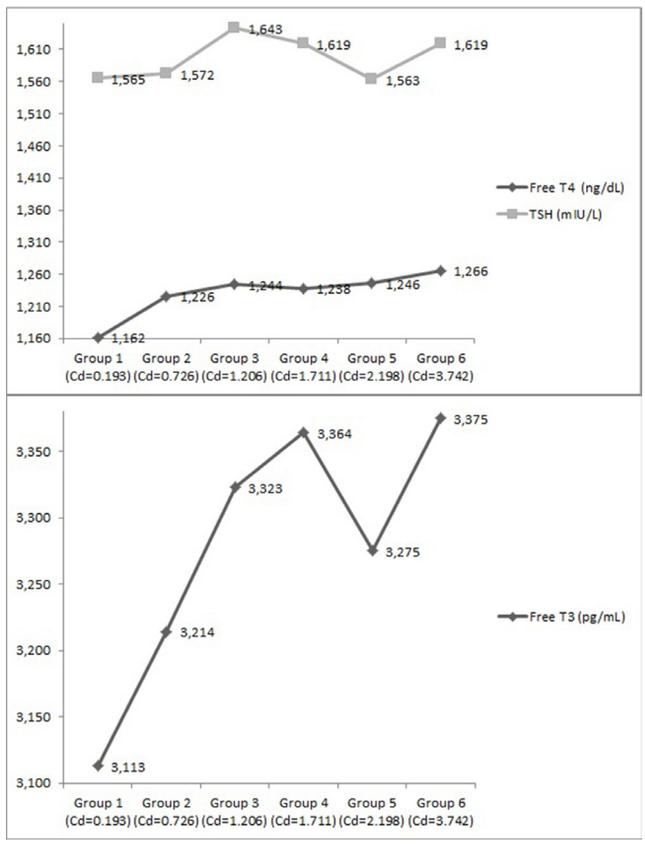

Figure 1. Comparision of serum free T3 and T4 levels in all groups.

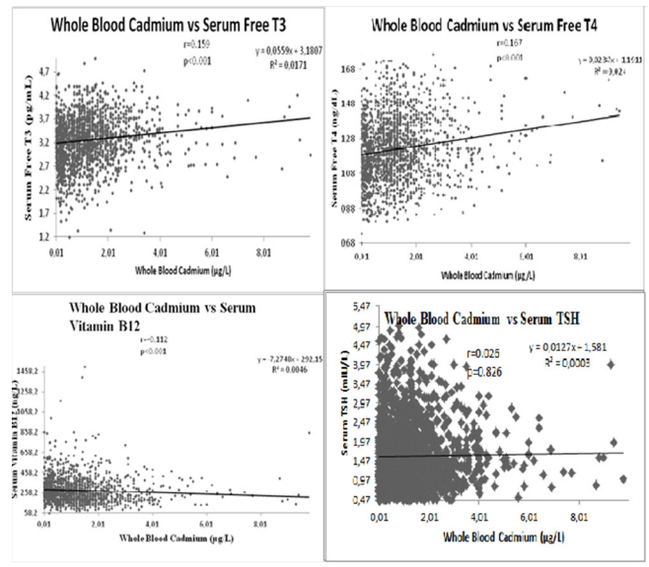

Figure 2. Correlation between whole blood cadmium and serum free T3, free T4, TSH, and vitamin B12 levels.

Discussion

Increasing use of metals in anthropogenic activities have led to toxic metal exposure. In recent years, many environmental and industrial chemicals have been identified as having a disrupting effect on the human endocrine system [16]. Even though the underlying mechanism of toxic effects of cadmium on thyroid functions is unknown, several studies have demonstrated the endocrine-disrupting effect of cadmium on thyroid hormones. There are several animal studies on cadmium-related thyroid dysfunction. Gupta et al. administered cadmium chloride to chickens for 15 days and demonstrated that this exposure decreased serum T3 concentration and hepatic 5'-monodeiodinase (5'D-I) and superoxide dismutase (SOD) activities (68.75%, 90.47%, and 20.81%, respectively). Administration of the antioxidant vitamin E (α-tocopherol, 5 mg/kg weight on alternate days) was reported as preventing cadmium-induced increase in lipid peroxidation [17]. In another experimental study, there were inconsistent results. Assessing the effect of lead and cadmium on endocrine status in cows naturally exposed to lead and cadmium in different industrial areas, the correlation between thyroidal hormones and the whole blood cadmium concentrations were found to be not significant (r = - 0.079 and – 0.48; P > 0.05). However, there was a positive correlation between blood lead and plasma T3 (r = 0.287) and T4 (r = 0.173) [18]. In a study to determine the effect of long-term, low-dose cadmium administration on thyroid functions in sheep, it was found that serum levels of T3, T4, free T3, free T4, and TSH significantly decreased in cadmium-treated sheep compared to a control group (p<0.05) [19] (Table 2).

Although the age range for this study was wide (18-70 years),

Table 2. Animal studies related with cadmium and thyroid hormone levels.

Number	Species	Method	Exposure Period	Results	Reference
1	Chicken	ND	15 days	Decrease	Gupta et al [17]
2	Cow	AAS	3 years	No change	Swarup et al [18]
3	Sheep	AAS	8 weeks	Decrease	Badiei et al [19]

ND= not defined, AAS=atomic absorption spectrometry.

there has been no specific reference range of thyroid hormone levels. In human studies there are some conflicting results among different studies. In a study group with a goiter diagnosis, cadmium was detected only in nodular goiter samples (n=65) [20]. In another study, cadmium in cord blood and TSH concentrations in neonatal blood were found to be significantly negatively correlated [21]. In a Japanese study, 35 inhabitants of the cadmium-polluted Kakehashi River area in Ishikawa Prefecture were compared to 60 inhabitants of a non-polluted area. T4 levels of females were found to be significantly lower while T3 levels of both genders were significantly higher than in controls [22]. Another study reported no association between concentrations of heavy metals and thyroid hormone levels [23]. In Germany, as part of an epidemiological study on exposure to a toxic waste incineration plant, Osius's group investigated the relation between blood concentrations of polychlorinated biphenyls (PCBs), lead, cadmium, mercury, and thyroid hormone status. Blood cadmium concentration was associated with increasing TSH and diminishing FT4 [24]. In an evaluation of the relationship between cadmium exposure and thyroid hormones in the National Health and Nutrition Examination Survey (NHANES) 2007-2008, urinary cadmium was found to be positively associated with total T3, total T4, free T3, and thyroglobulin (Tg) [3] (Table 3).

In this study, we found a positive correlation between whole blood cadmium levels and serum thyroid hormones. Serum vitamin B12 levels were inversely correlated with cadmium exposure. This finding may indicate that high levels of cadmium can accelerate the elimination process of vitamin B12 [25]. This might be an explanation for the lower serum vitamin B12 levels in cadmium-exposed groups. Also in this study, there was a negative and positive correlation between cadmium and serum ALT. Further studies must be performed to establish this association.

Table 3. Human studies related with cadmium and thyroid hormone levels.

Number	Number of samples	Method	Follow-up Period	Results	Reference
1	5418	ICP-MS	ND	Decrease	Chen et al [3]
2	65	IC	ND	No change*	Błazewicz et al [20]
3	24	ICP-MS	1 year	No change**	Iijima et al [21]
4	105	ND	ND	Increase***	Nishijo et al [22]
5	198	ICP-MS	2 years	No change	Maervoet et al [23]
6	320	AAS	1 year	Decrease	Osius et al [24]

ND= not defined, AAS=atomic absorption spectrometry, IC=ion-chromatography, ICP-MS=inductively coupled plasma mass spectrometry. * Found in only one goitre tissue. ** Negative correlation with TSH but not free T4. *** Only in T3

Conclusion

This study found a positive correlation between whole blood cadmium levels and serum thyroid hormones. The alterations in these hormone levels might be due to a blockage in the peripheral conversion step. Although serum TSH levels were found not to be statistically significant between groups, a counteractivation of thyroid stimulation and thyroid hormone (free T3 and free T4) release may occur as a compensation mechanism.

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Competing interests

The authors declare that they have no competing interests.

References

1. Kothinti R, Blodgett A, Tabatabai NM, Petering DH. Zinc finger transcription factor Zn3-Sp1 reactions with Cd2+. Chem Res Toxicol 2010;23(2):405-12.
2. Henson MC, Chedrese PJ. Endocrine disruption by cadmium, a common environmental toxicant with paradoxical effects on reproduction. Exp Biol Med (Maywood) 2004;229(5):383-92.
3. Chen A, Kim SS, Chung E, Dietrich KN. Thyroid hormones in relation to lead, mercury, and cadmium exposure in the National Health and Nutrition Examination Survey, 2007-2008. Environ Health Perspect 2013;121(2):181-6.
4. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev 2002;23:28-89.
5. Köhrle F. Local activation and inactivation of thyroid hormones: the deiodinase family. Mol Cell Endocrinol 1999;151:103-19.
6. Boas M, Feldt-Rasmussen U, Skakkebaek NE, Main KM. Environmental chemicals and thyroid function. Eur J Endocrinol 2006;154(5):599-611.
7. Mori K, Yoshida K, Hoshikawa S, Ito S, Yoshida M, Satoh M, et al. Effects of perinatal exposure to low doses of cadmium or methylmercury on thyroid hormone metabolism in metallothionein-deficient mouse neonates. Toxicology 2006;228(1):77-84.
8. Wade MG, Parent S, Finnsan KW, Foster W, Younglai E, McMahon A, et al. Thyroid toxicity due to subchronic exposure to complex mixture of 16 organochlorines, lead and cadmium. Toxicol Sci 2002;67(2):207-18.
9. Messaudi I, Hammauda F, El Heni J, Baati T, Said K, Kerkeni A. Reversal of cadmium-induced oxidative stress in rat erythrocytes by selenium, zinc or their combination. Exp Toxicol Pathol 2010;62(3):281-8.
10. Shaikh ZA, Vu TT, Zaman K. Oxidative stress as a mechanism of chronic cadmium-induced hepatotoxicity and renal toxicity and protection by antioxidants. Toxicol Appl Pharmacol 1999;154:256-63.
11. Lee WK, Torchalski B, Kohistani N, Thevenod F. ABCB1 protects kidney proximal tubule cells against cadmium-induced apopitosis: Role of cadmium and ceramide transport. Toxicol Sci 2011;121(2):343-56.
12. Thompson JM, Hipwell E, Loo HV, Bnnigan JG. Effects of cadmium on cell death and cell proliferation in chick embryos. Reprod Toxicol 2005;20:539-48.
13. Jancic SA, Stosic BZ. Cadmium effects on the thyroid gland. Vitam Horm 2014;94:391-425.
14. Kashiwagi K, Nobuaki F, Kitamura S, Ohta S, Sugihara K, Utsumi K, et al. Disruption of Thyroid Hormone Pollutants. Journal of'Health Science 2009; 55(2):147-60.
15. Bal C, Karakulak U, Gündüzöz M, Ercan M, Tutkun E, Yılmaz ÖH. Evaluation of Subclinical Inflammation with Neutrophil Lymphocyte Ratio In Heavy Metal Exposure. J Clin Anal Med 2016;7(5): 643-7.
16. Yang M, Park MS, Lee HS. Endocrine disrupting chemicals: human exposure and health risks. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 2006;24(2):183-224.
17. Gupta P, Kar A. Cadmium induced thyroid dysfunction in chickens: hepatic type I 5'-monodeiodinase activity and role of lipid peroxidation. Comp Biochem Physiol C Pharmacol Toxicol Endocrinol 1999;123(1):39-44.
18. Swarup D, Naresh R, Varshney VP, Balagangatharathilogar M, Kumar P, Nandi D, et al. Changes in plasma hormones profile and liver function in cows naturally exposed to lead and cadmium around different industrial areas. Res Vet Sci 2007;82(1):16-21.
19. Badiei K, Nikghadam P, Mostaghni K. Effect of cadmium on thyroid function in sheep. Comp Clin Pathol 2009;18:255-9.
20. Błazewicz A, Dolliver W, Sivsammye S, Deol A, Randhawa R, Orlicz-Szczesna G, et al. Determination of cadmium, cobalt, copper, iron, manganese, and zinc in thyroid glands of patients with diagnosed nodular goitre using ion chromatography. J Chromatogr B Analyt Technol Biomed Life Sci 2010;878(1):34-8.
21. Iijima K, Otoke T, Yoshinaga J, Ikegami M, Suzuki E, Naruse H, et al. Cadmium,

lead and selenium in codr blood and thyroid hormone of newborns. Biol Trace Elem Res 2007;199(1):10-8.
22. Nishijo M, Nakagawa H, Morikawa Y, Tabata M, Senma M, Miura K, et al. A study of thyroid hormone levels of inhabitants of the cadmium-polluted Kakehashi River basin .Nihon Eiseigaku Zasshi 1994;49(2):598-605.
23. Maervoet J, Vermeir G, Covaci A, Van Larebeke N, Koppen G, Schoeters G, et al. Association of thyroid hormone concentrations with levels of organochlorine compounds in cord blood of neonates. Environ Health Perspect 2007;115(12):1780-6.
24. Osius N, Karmaus W, Kruse H, Witten J. Exposure to polychlorinated biphenyls and levels of thyroid hormones in children. Environ Health Perspect 1999;107(10):843-9.
25. Merlini M. Hepatic storage alteration of vitamin b12 by cadmium in a freshwater fish. Bulletin of Environmental Contamination and Toxicology 1978; 19(1):767–71.

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